DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

August 22, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David W. Ammann
President/Chairman of the Board
Alphamed, Inc.
3000 Northwoods Parkway
Suite 185
Norcross, Georgia 30071

WARNING LETTER

Dear Mr. Ammann:

An inspection of your firm was conducted between June 24 and July 18, 1997, by Investigator P. Wayne Moy. Our investigator found that you are manufacturing and distributing ambulatory infusion pumps, bag reservoirs, and infusion sets. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Investigator Moy documented several significant deviations from the Good Manufacturing Practice for Medical Devices (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 820. These observations would also be violations of the Quality System Regulation, (21 CFR), Part 820. These deviations cause the devices you manufacture and distribute to be adulterated within the meaning of Section 501(h) of the Act.

You have failed to establish and implement a quality assurance program that is appropriate for the medical devices manufactured and distributed by your firm. Quality assurance procedures in place failed to ensure that your devices conformed with finished device specifications prior to release. You have failed to appropriately validate the sterilization and packaging processes in use. You could not provide documented evidence which established a high degree of assurance that the sterilization and packaging processes in use are effective and could consistently produce a product meeting its predetermined sterility specifications and quality attributes.

The current ethylene oxide cycle utilized to sterilize bag reservoirs was determined to be validated, even though two of the four half cycle validation runs failed to meet the microbial challenge acceptance criteria in the protocol. There was also no documentation available which

would indicate that the 70 ml. or 250 ml. bag reservoirs were ever evaluated to determine their comparability to the most difficult product to sterilize in the family group utilizing the above cycle.

The sterility failure investigations of the two half cycle failures above were deficient in that they did not include any review of the device history records, manufacturing procedures, sterilization records, processing procedures, maintenance history of the sterilizer and ancillary equipment, sterility testing procedures, or environmental control data at the testing laboratory. No D value determinations were made for all isolates and all isolates were not identified. Similar problems were noted in the sterility failure investigation of BR70 Bag Reservoir, Lot H123401 which was sterilized in load C94-0372.

Although the sterilization cycle for infusion sets was reportedly revalidated in March 1997, no Alphamed infusion sets were involved in the study. Your contract sterilizer refused to furnish any information describing what products were actually used in this revalidation study. No revalidation of the sterilization cycle utilized for bag reservoirs has been conducted since the initial 1994 study.

You could provide no documentation that would indicate that the [redacted] sealer used to seal the bag reservoir pouches has been validated. In fact, your contract packager stated that the [redacted] sealer had not been validated. You could provide no documentation which would indicate that seal integrity studies had been performed on the 70 ml. or 250 ml. bag reservoir pouches after multiple sterilizations. [redacted] has the authority to resterilize products and this has occurred in the past with this product.

The validation performed on the [redacted] Pouch Sealers was deficient in that it did not include any pouches of the size used for the Alphamed infusions sets. The validation that was performed utilized a smaller pouch size not in use at Alphamed. No studies were performed on the effects of sterilization on the pouch seal integrity. All studies performed also used a bag size not in use at Alphamed. No formal assessment has been made as to the effects of sterilization or resterilization on the seal integrity of the larger pouches used by Alphamed.

You have failed to establish appropriate written procedures for finished device inspection to assure that all device specification and requirements are met prior to release for distribution. A review of your records revealed that three of the eight released lots of bag reservoirs had not been tested for pyrogens. No written procedures had been established and no requirement had been implemented, that would assure that each lot of these products was tested for pyrogens prior to release. Each of these products included the statement "NON-PYROGENIC" on the package labeling.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. At the close of the inspection, the Inspectional Observations (FDA 483) was issued to and discussed with you. The specific violations noted in this letter and in the FDA 483 are symptomatic of serious underlying problems in your firm's quality assurance systems. You are responsible for

investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

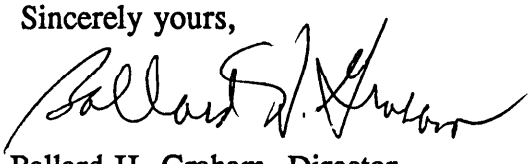
Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submission of devices to which the GMP deficiencies are reasonably related will be cleared until these violations have been corrected. Also, no request for Certificates for Products for Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory actions being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your response should address any product currently in distribution which has not been properly tested. Your response should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

We are in receipt of your July 31 response to the FDA 483. Investigator Moy has reviewed this response and it addressed the majority of concerns raised during the inspection. The actions discussed, if implemented, would appear to correct the deviations noted. You may reference that response if you feel it adequately addresses any of the points mentioned in this letter. Please keep us apprised of additional corrective measures implemented and any changes in the proposed dates for correction. These corrections will be verified during the next inspection of your facility. This inspection will be scheduled to correlate with the completion dates discussed in your response.

Sincerely yours,



Ballard H. Graham, Director
Atlanta District